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ORIGINAL ARTICLE

Quantum chemical investigation of the molecular structure of some 2,3-dihydro-1,4-diazepines and related molecules

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AM1;
PM3;
1,4-Diazepines;
Tautomerism

Abstract Accurate ab-initio and semi-empirical molecular orbital calculations with full geometry optimization were performed on the various tautomeric forms of some 2,3-dihydro-1,4-diazepines and related molecules. The highly accurate ab-initio calculations at the HF/6–31G** level with Möller-Plesset Second-Order Perturbation Theory (MP2) refinement clearly established the higher stability of the enamine tautomer of the 1,4-diazepine ring over the di-imine form by 27.786 kJ/mol, whereas the semi-empirical calculations at the NDDO level (AM1 and PM3) predicted comparable energies within reported errors of the two methods. However, both ab-initio and semi-empirical NDDO methods predicted similar geometries in agreement with observed geometrical parameters. The AM1 calculations predicted small energy differences among the three tautomeric forms of 2,3-dihydro-5-methyl 7-phenyl 1,4-diazepine with the more polar enamine tautomer being the more stable tautomer in the half-chair conformation which is likely to predominate in polar media through stabilizing intermolecular solute-solvent interactions.

1. Introduction

The medicinal success of 1,4-benzodiazepines I (Fig. 1) (Sternbach et al., 1963, 1964; Rudzik et al., 1973; Mattila and Larni, 1980; Tallman et al., 1980; Rall, 1990) continues to stimulate considerable interest (Cazaux et al., 1983; Scahill and Smith, 1983; Salman et al., 1986; Gilman et al., 1990, 1993; Hamdi and Ahmed, 1993, 1996; Zycov et al., 1993; Pihlaja et al., 1997; Simeonov et al., 1997; Zahra et al., 2003; Venkatraj and Jeyaraman, 2006; Meanwell and Walker, 2008; Thakur et al., 2010) in this important class of N-heterocyclic compounds and related systems. The well-documented dependence of the biological activity of these systems on the stereochemistry of the seven-membered ring system (Fryer et al., 1986) is largely responsible for the continued interest in the study of the tautomerism of the 1,4-diazepines using a diversity of experimental and theoretical techniques such as NMR, X-ray diffraction and molecular mechanics calculations.

These studies have indicated that the chair-form of the seven-membered system has the lowest energy. However, a

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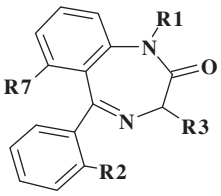
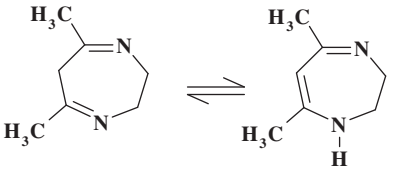
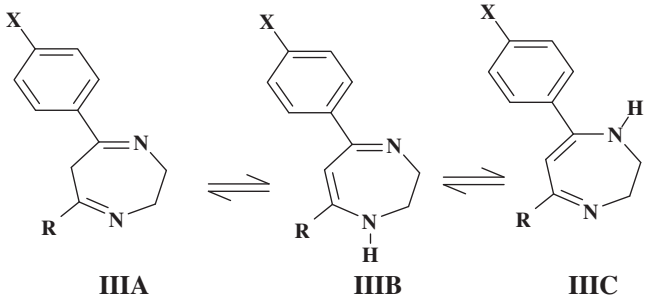


I
diazepam



IIA IIB

2,3-dihydro- 5,7-dimethyl 1,4-diazepine



IIIA IIIB IIIC

2,3-dihydro- 5-methyl 7-aryl 1,4-diazepine

Figure 1 The structures of some 1,4-diazepines.

rapid inter-conversion involving the boat-shape conformation was also established by NMR spectroscopy for the diazepine ring in some 1,4-benzodiazepines and related 2,4-benzodiazepines (Venkatraj and Jeyaraman, 2006).

Although early theoretical investigations have used the relatively faster but inheritably less rigorous molecular mechanics (MM) methods, more recent reports have used the relatively more accurate semi-empirical methods particularly AM1 and PM3 which provide a satisfactory account of the molecular geometries and relative energies of large molecular systems (Dewar et al., 1985, 1993; Stewart, 1989; Feller and Peterson 1998). Nevertheless, even with the current advances in computational techniques and widely available fast computers, the use of the more accurate ab-initio methodologies is prohibitively restricted to small and medium sized molecular systems unless highly sophisticated and dedicated parallel computing facilities are employed.

In this work, a combination of standard semi-empirical techniques (AM1 and PM3) and accurate ab-initio MO calculations are employed for the determination of stabilities and equilibrium geometries of the various tautomeric forms of some representative 1,4-diazepines. Typical Structures are shown in Fig. 1.

Table 1 Selected bond lengths (Å), bond angles (°) and dihedral angles (°) for tautomer II(A) of the 2,3-dihydro 1,4-diazepine parent system. For key, see Fig. 1.

	Quantum chemical calculations				
	Ab-initio			Semi-empirical	
	3-21G	6-31G**	6-31G** MP2	AM1	PM3
Bond lengths (Å)					
N(1)–C(2)	1.4729	1.4526	1.4646	1.4292	1.4551
C(2)–C(3)	1.5373	1.5254	1.5252	1.5369	1.5253
C(3)–N(4)	1.4727	1.4499	1.4630	1.4290	1.4549
N(4)–C(5)	1.2522	1.2496	1.2846	1.2763	1.2831
C(5)–C(6)	1.5152	1.5189	1.5184	1.4918	1.4898
C(6)–C(7)	1.5153	1.5147	1.511	1.4918	1.4898
C(7)–N(1)	1.2522	1.2495	1.2853	1.2763	1.2832
N(4)–H	–			–	–
C(6)–H	1.09	1.091	1.1025	1.128	1.111
N(1)···N(4)	3.236	3.181	3.182	3.188	3.165
Bond angles (°)					
N(1)–C(2)–C(3)	114.53	113.240	111.355	117.772	115.564
C(2)–C(3)–N(4)	114.622	118.201	118.680	117.875	115.631
C(3)–N(4)–C(5)	123.795	124.663	122.909	125.608	126.855
N(4)–C(5)–C(6)	131.755	131.248	130.980	133.694	131.486
C(5)–C(6)–C(7)	121.594	116.947	114.377	119.115	121.034
C(6)–C(7)–N(1)	131.637	126.720	125.725	133.635	131.392
C(5)–C(6)–H	106.862	108.576	109.304	107.089	106.751
C(7)–C(6)–H	106.918	109.045	109.511	107.085	106.751
C(5)–N(4)–H	–	–	–	–	–
H–C(2)–H	107.79	106.893	109.083	107.203	106.539
H–C(6)–H	105.152	105.592	106.015	107.002	105.532
Dihedral angles (°)					
C(5)–C(6)–C(7)–N(1)	−13.553	−50.098	36.255	−10.891	−11.779
C(6)–C(7)–N(1)–C(2)	1.9798	0.978	−57.585	0.487	0.951
C(7)–N(1)–C(2)–C(3)	48.037	67.380	1.685	41.908	44.742
C(5)–N(4)–C(3)–C(2)	47.113	19.923	−73.377	41.260	43.919
N(1)–C(2)–C(3)–N(4)	−78.037	−72.149	71.569	−66.450	−70.112
H–C(7)–N(1)–C(2)	179.477	179.699	−178.732	178.866	179.207

2. Computational methods

Ab-intio calculations were performed with the Gaussian 03W package (Frisch et al., 2004). Semi-empirical calculations were performed using the original parameter set of the MOPAC 6 package (Dewar et al., 1985; Stewart, 1989). The geometries of the various tautomeric forms of 2,3-dihydro-1,4-diazepines are obtained using full geometry optimization at both the semi-empirical and ab-initio methods. Ab-initio full geometry optimization was carried out using the GDIIS method (Pulay, 1980, 1982; Csaszar and Pulay, 1984; Farkas, 1995; Farkas and Schlegel 1999) at the HF/3–21G, HF/6–31G** and HF/6–31G** MP2 levels.

The ground state molecular energies and stabilities of these systems were computed at a higher level of a basis set using extended HF/6–31G** basis set with diffuse functions and refined using Möller-Plesset Second-Order Perturbation Theory (MP2) calculations aimed at accounting for the correlation energy.

Table 2 Selected bond lengths (Å), bond angles (°) and dihedral angles (°)for tautomer II(B) of the 2,3-dihydro 1,4-diazepine parent system. For key, see Fig. 1.

	Quantum chemical calculations				
	Ab-initio			Semi-empirical	
	3-21G	6-31G**	6-31G** MP2	AM1	PM3
Bond lengths (Å)					
N(1)–C(2)	1.4663	1.4452	1.4515	1.4280	1.4555
C(2)–C(3)	1.550	1.5345	1.5482	1.5454	1.530
C(3)–N(4)	1.4559	1.4459	1.4496	1.433	1.4738
N(4)–C(5)	1.3579	1.3537	1.3642	1.374	1.4148
C(5)–C(6)	1.33935	1.3452	1.3708	1.3565	1.3453
C(6)–C(7)	1.4577	1.4662	1.4516	1.4474	1.4506
C(7)–N(1)	1.266	1.261	1.3023	1.2876	1.2918
N(4)–H	0.9956	0.9938	1.0129	0.9956	0.9970
C(6)–H	1.072	1.075	1.0879	1.102	1.098
N(1)–N(4)	3.1952	3.1977	3.2451	3.201	3.217
Bond angles (°)					
N(1)–C(2)–C(3)	121.111	115.574	112.606	116.505	113.537
C(2)–C(3)–N(4)	112.037	112.572	112.444	116.318	115.384
C(3)–N(4)–C(5)	123.678	123.225	121.707	123.504	120.786
N(4)–C(5)–C(6)	129.083	128.675	127.886	129.387	129.273
C(5)–C(6)–C(7)	128.334	128.498	129.139	127.374	128.941
C(6)–C(7)–N(1)	130.979	131.135	130.272	131.588	129.153
C(5)–C(6)–H	116.601	116.190	115.221	117.565	117.13
C(7)–C(6)–H	115.061	115.286	115.611	115.060	113.918
C(5)–N(4)–H	118.24	116.750	116.447	115.493	110.299
H–C(2)–H	108.311	107.160	108.104	107.535	106.699
Dihedral angles (°)					
C(5)–C(6)–C(7)–N(1)	−16.145	−16.193	−20.293	−12.225	−15.405
C(6)–C(7)–N(1)–C(2)	−1.497	−1.996	−0.968	0.4478	2.1755
C(7)–N(1)–C(2)–C(3)	52.814	52.134	59.554	45.416	48.427
C(5)–N(4)–C(3)–C(2)	49.614	51.539	43.875	44.509	47.023
N(1)–C(2)–C(3)–N(4)	−79.812	−79.756	−87.871	−72.703	−78.175
H–C(7)–N(1)–C(2)	177.5	177.462	177.452	178.796	179.99

3. Results and discussion

The stereochemistry of the seven-membered ring system of 1,4-diazepine plays an important role in the biological activity of these molecules (Fryer et al., 1986). Although earlier studies on these systems have employed the less accurate molecular mechanics and semi-empirical methods a more accurate account of the stereochemistry of these systems is required.

The 2,3-dihydro-1,4-diazepine parent system may exist in two tautomeric forms IIA (di-imine) and IIB (enamine) (see Fig. 1). In the present investigation, the molecular geometries of the parent system in the two possible tautomeric forms are calculated using large extended HF/6–31G** basis set with diffuse functions. In all cases, full geometry optimization was performed with no geometrical constraints in a stepwise fashion starting with HF/3–21G to get an initial geometry which is then refined using the HF/6–31G** basis set. This level of ab-initio calculation is known to give accurate molecular geometries and conformation energies (St-Amant et al., 1995; Jensen, 1999; Cramer, 2002). The accurate molecular geometries and molecular energies of the two forms at the HF/6–31G** level are then further refined using the Möller-Plesset second-order perturbation theory (MP2) (Bartlett, 1981) with full geometry optimization .

The ab-initio HF/3–21G, HF/6–31G** and HF/6–31G** MP2 calculated molecular geometries of the two forms of the parent system are summarized in Tables 1 and 2. For comparison purposes, the calculated geometrical parameters from both the AM1 and PM3 semi-empirical methods are also listed in Tables 1 and 2. The three-dimensional ray-traced ball and stick diagrams based on the ab-initio geometries are displayed in Fig. 2.

In the di-imino form (tautomer IIA), the ab-initio calculated C(7)-N(1) bond length of ∼1.25 , at the 6–31G** level, is comparable with the standard azomethine C═N bond length of 1.24 . Whereas, in the enamine tautomer IIB, the 6–31G** calculations gave an azomethine type C═N value of 1.26 and an enamine type C–N value of 1.35 in agreement with experimental values of similar CN bond types. The enamine C–N value is intermediate between the single bond length of 1.47 and the double bond length of 1.24 . The seven-membered 1,4-diazepine ring is predicted by the present ab-initio calculation to exist in the half-chair conformation where the C(2) and C(3) atoms are shifted above and below the ring plane. The N(4), C(5), C(6), C(7) and N(1) atoms are nearly planar but are twisted by ∼13° (see Fig. 2). It is noteworthy, that the HF/6–31G** MP2 calculations gave slightly longer bond lengths and expanded ring systems in comparison with HF/6–31G**. This is in accord with the observation (Stewart et al., 1994) that HF/6–31G** & HF/6–31G** MP2 levels show different geometries with MP2 geometries that compare well with observed geometries of nucleic acid bases.

The semi-empirical AM1 and PM3 methods predict similar molecular structures for the two tautomers to those predicted by the ab-initio methods but may differ slightly in terms of the calculated bond lengths and bond angles with the PM3 set compares favorably with the MP2 geometries.

The ab-initio calculated bond lengths and bond angles are, in general (St-Amant et al., 1995; Jensen, 1999; Cramer, 2002), more accurate than those calculated by the AM1 and PM3 methods. At the HF/3–21G level, the bond lengths are generally reproduced to within ±0.01 , while the AM1 method gives bond lengths accurate to within ±0.03 . The bond angles are reproduced to within ±3°, whereas the dihedral angles are usually subject to larger errors at both the ab-initio and semi-empirical levels of theory.

The ground state molecular energies and net charges calculated by semi-empirical (AM1 and PM3) and ab-initio methods are summarized in Table 3 for the two tautomers of the parent system.

The ab-initio calculations at all levels clearly indicate that the enamine form (tautomers IIB) is energetically more favored and is more stable than the di-imino form (IIA) by 12.682, 4.513 and 6.641 kcal/mol for the HF/3–21G, HF/6–31G**, and HF/6–31G**MP2 calculations, respectively. The calculated energy differences at all levels are much greater than the reported errors at these levels. At the HF/6–31G** MP2 level of *ab initio* theory, the calculated energies are accurate enough for most chemical applications, particularly for conformation energies of tautomers.

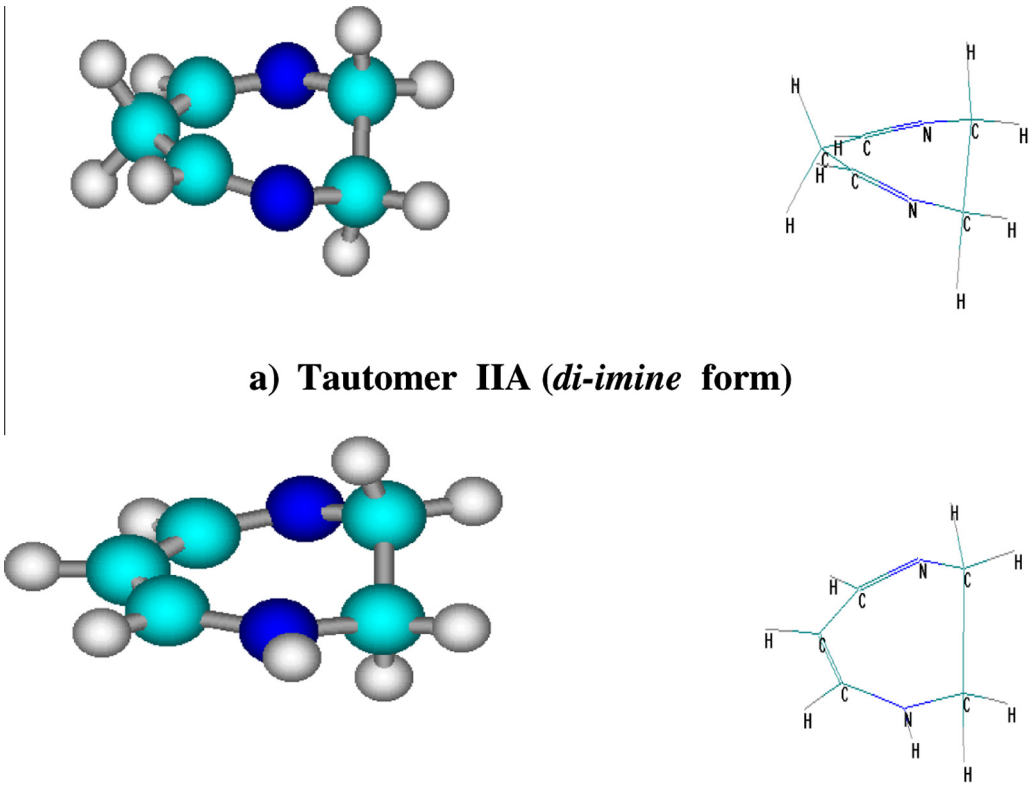
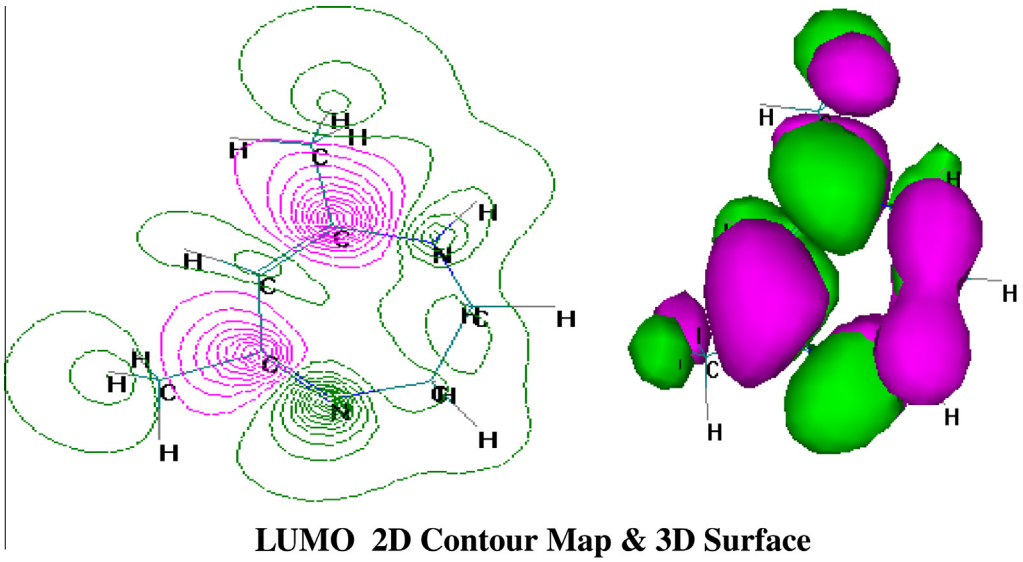


Figure 2 Ground state geometry of the parent 1,4-diazepine system computed by ab-initio MO method.

Table 3 Ground state energies and molecular properties of the parent system.

	Ab-initio			Semi-empirical	
	HF/3–21G	HF/6–31G**	HF/6–31G** MP2	AM1	PM3
Tautomer IIA					
Total Energy kcal/mol	−188967.751	−190043.418	−190652.087 (−612.547)*	−26834.332 $\Delta_f H^o$ = 31.510	−23972.896 $\Delta_f H^o$ = 31.029
LUMO eV	4.62195	1.02777	1.01689	0.87481	0.61675
HOMO eV	−9.92608	−10.22142	−10.29570	−9.91166	−9.79284
LUMO–HOMO eV	14.54803	11.24919	11.31259	10.78647	10.40959
Net Charges: N1	−0.57863	−0.20411	−0.2062	−0.18466	−0.12112
N4	−0.57796	−0.19451	−0.2063	−0.18445	−0.12110
C5	0.16235	0.03447	0.01784	−0.06230	−0.07536
C6	−0.60187	−0.57863	−0.55946	−0.19851	−0.10000
C7	0.16280	0.01460	−0.02509	−0.06218	−0.07549
Dipole Moment (Debye)	1.521	2.208	2.474	1.554	1.485
Tautomer IIB					
Total Energy kcal/mol	−188980.433	−190047.931	−190658.728 (−614.068)*	−26833.593 $\Delta_f H^o$ = 32.249	−23971.347 $\Delta_f H^o$ = 32.578
LUMO eV	3.935326	0.89634	0.89471	0.58719	0.08509
HOMO eV	−7.994020	−8.24478	−8.28669	−8.54060	−8.77959
LUMO–HOMO eV	11.929346	9.14112	9.18140	9.12779	8.86468
Net Charge: N1	−0.882608	−0.24508	−0.25636	−0.32097	0.04922
N4	−0.612828	−0.59919	−0.55808	−0.21815	−0.14747
C5	0.153560	0.20314	0.13549	−0.00183	−0.01054
C6	−0.415308	−0.55258	−0.50323	−0.32198	−0.23706
C7	0.213421	−0.06542	−0.09146	0.03230	−0.09949
Dipole Moment (Debye)	4.127	4.065	4.090	3.430	2.876

* MP2 correlation energy value is included in the total energy.



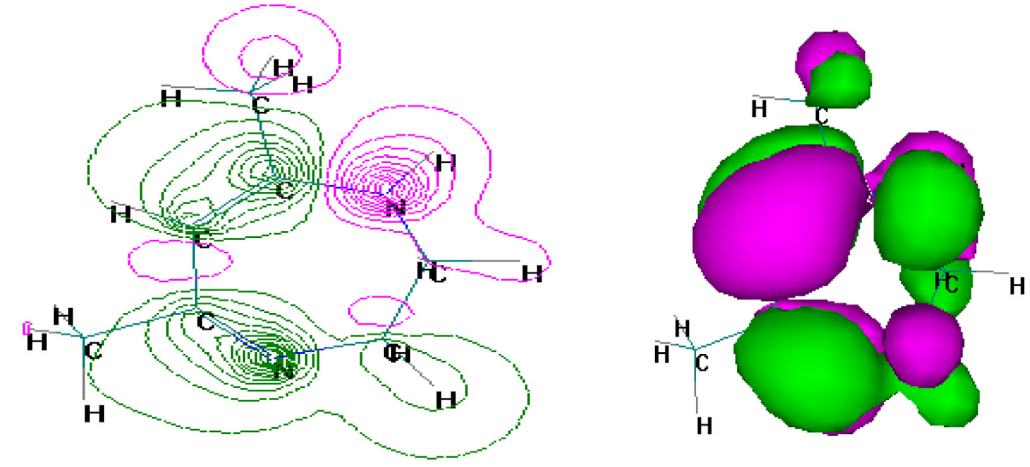
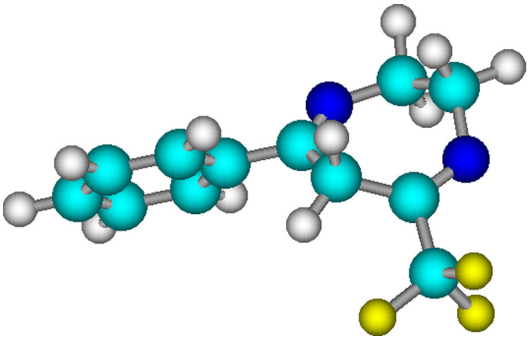


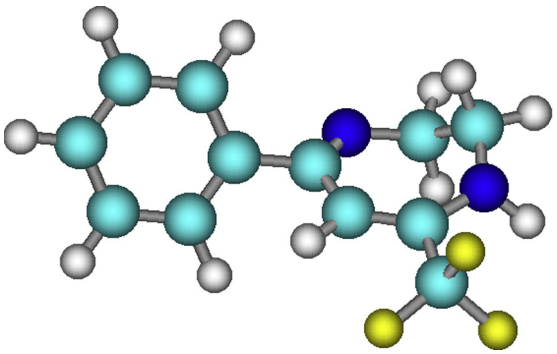
Figure 3 Ab-initio HF/6–31G** HOMO and LUMO maps of 2,3-dihydro-5,7-dimethyl-1,4-diazepine (Tautomer IIB).



Tautomer III A (di-imine form)

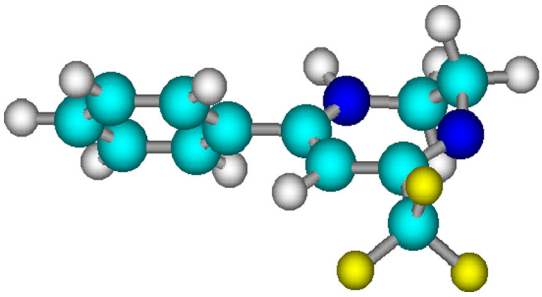
Total Energy = -82024.17 kcal/mol
$\Delta_f H^o$ = -91.41 kcal/mol
Dipole Moment = 3.057D

Figure 4 AM1 optimized geometry of 2,3-dihydro-5-trifluoromethyl-7-phenyl-1,4-diazepine (IIIA).



Tautomer III B (enamine form)

Total Energy = -82025.39 kcal/mol
$\Delta_f H^o$ = -92.63 kcal/mol
Dipole Moment = 1.677 D



Tautomer III C (enamine form)

Total Energy = -82027.14 kcal/mol
$\Delta_f H^o$ = -94.38 kcal/mol
Dipole Moment = 6.592 D

Figure 5 AM1 optimized geometry 2,3-dihydro-5-trifluoromethyl-7-phenyl-1,4-diazepine (IIIB and IIIC).

The present HF/6–31G**MP2 calculation clearly established the higher stability of the enamine form of the diazepine ring over the di-imine form by 27.786 kJ/mol.

On the other hand, the present semi-empirical calculations at the NDDO level (AM1 and PM3) predicted the two tautomers to have nearly the same energies within the reported errors of the two methods. Thus, although these semi-empirical methods are accepted now as being reliable computational techniques for molecular geometries and conformational energies, the use of ab-initio methods remains the most reliable for predicting accurate molecular energies.

The HOMO-LUMO energy gap calculated by the ab-initio methods is considerably higher than that calculated by the semi-empirical methods. However, at both levels of theory the di-imino tautomer (IIA) is predicted to have a higher gap in comparison with the enamine form (IIB). This indicates a higher degree of π-conjugation in tautomer IIB. The ab-initio HF/6–31G** 2D contour maps and 3D surfaces of the HOMO and LUMO molecular orbitals of the enamine form (tautomer IIB) of 2,3-dihydro-5,7-dimethyl-1,4-diazepine are displayed in Fig. 3. In general, the HOMO level is far more susceptible to structural changes than the LUMO level. This observation is consistent with observed Photoelectron spectra of a series of 1,4-benzodiazepines derivatives (Zycov et al., 1993), where the HOMO showed greater susceptibility to the effects of substituent and structural changes.

In addition, the enamine tautomer (IIB) is also predicted to have a more polar charge distribution as evidenced by higher charge separation (see Table 3) and a higher calculated value of the dipole moment. At the HF/6–31G** MP2 level, the enamine form (tautomer IIB) is predicted to have a dipole moment of 4.09 D in comparison with a value of 2.47 D calculated for the di-imino form (tautomer IIA).

The AM1 calculated geometries of the three tautomeric forms of 2,3-dihydro-5-methyl 7-phenyl 1,4-diazepine (III) are depicted in Figs. 4 and 5. While the AM1 preferred conformation of the di-imine form (tautomer IIIA) is the boat conformation, that of the two enamine forms (tautomers IIIB and IIIC) is the half-chair conformation. However, the energy differences among the three tautomers are small with tautomer IIIC having the lowest energy and is the most stable of the three forms. The later form is also the most polar with a dipole moment value of 6.592 D. Based on these observations, it was concluded that the more polar enamine tautomer IIIC in the half-chair conformation will predominate in polar media through stabilizing inter-molecular solute-solvent interactions.

4. Conclusions

The present study has demonstrated the benefits of combining accurate ab-initio MO calculations for molecular energies and stabilities, and standard semi-empirical NDDO parameterized computational schemes (AM1, PM3) for molecular geometries as an effective framework for investigating large molecular systems. The ab-initio calculations at all levels clearly indicate that the enamine form, in the half-chair conformation, is energetically more favored and is more stable than the di-imino form. At the HF/6–31G**MP2 level, the enamine tautomer is energetically favored over the di-imine form by 27.786 kJ/mol. Semi-empirical methods (AM1 and PM3) offer a computationally less-expensive way of calculating reasonably accurate molecular geometries and ground state properties, particularly for large molecular systems.

Acknowledgments

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References

Bartlett, R.J., 1981. Ann. Rev. Phys. Chem. 32, 359.
Cazaux, L., Vidal, C., Pasdeloup, M., 1983. Org. Magn. Reson. 21, 190.
Csaszar, P., Pulay, P., 1984. J. Mol. Struct. THEOCHEM 114, 31.
Cramer, C.J., 2002. Essentials of Computational Chemistry. John Wiley & Sons.
Dewar, M.J.S., Zoebisch, E.G., Healy, E.F., Stewart, J.J.P., 1985. J. Am. Chem. Soc. 107, 3902.
Dewar, M.J.S., Jie, C., Yu, J., 1993. Tetrahedron 49, 5003.
Farkas, Ö., 1995. PhD (CSc) Thesis, Eötvös Loránd University and Hungarian Academy of Sciences, Budapest, (in Hungarian).
Farkas, Ö., Schlegel, H.B., 1999. J. Chem Phys. 111, 10806.
Feller, D., Peterson, K.A., 1998. J.Chem. Phys. 108, 154.
Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Montgomery, Jr., J. A., Vreven, T., Kudin, K. N., Burant, J. C., Millam, J. M.,Iyengar, S. S., Tomasi, J., Barone, V., Mennucci, B., Cossi, M., Scalmani, G., Rega, N., Petersson, G. A., Nakatsuji, H., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Klene, M.,Li, X., Knox, J. E., Hratchian, H. P., Cross, J. B., Adamo, C., Jaramillo, J., Gomperts, R.,Stratmann, R. E., Yazyev, O., Austin, A. J., Cammi, R., Pomelli, C., Ochterski, J. W.,Ayala, P. Y., Morokuma, K., Voth, G. A., Salvador, P., Dannenberg, J. J., Zakrzewski, V. G., Dapprich, S., Daniels, A. D., Strain, M. C., Farkas, O., Malick, D. K., Rabuck, A. D., Raghavachari, K., Foresman, J. B., Ortiz, J. V., Cui, Q., Baboul, A. G., Clifford, S.,Cioslowski, J., Stefanov, B. B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I.,Martin, R. L., Fox, D. J., Keith, T., Al-Laham, M. A., Peng, C. Y., Nanayakkara, A.,Challacombe, M., Gill, P. M. W., Johnson, B., Chen, W., Wong, M. W., Gonzalez, C.,and Pople, J. A., 2004. Gaussian 03, Revision C.01, Gaussian, Inc., Wallingford CT.
Fryer, R.I., Cook, C., Gilman, N.W., Walser, A., 1986. Life Sci. 39, 1947.
Gilman, N.W., Rosen, P., Earley, J.V., Cook, C.M., Todaro, L.J., 1990. J. Am. Chem. Soc. 112, 3969.
Gilman, N.W., Rosen, P., Earley, J.V., Cook, C.M., Blount, J.F., Todaro, L.J., 1993. J. Org. Chem. 58, 3285.
Hamdi, S.T., Ahmed, K.Y., 1993. Canadian J. Appl. Spectrosc 38, 82–88.
Hamdi, S.T., Ahmed, K.Y., 1996. Monatshefte für Chemie 127, 1013–1019.
Jensen, F., 1999. Introduction to Computational Chemistry. John Wiley & Sons.
Mattila, M.A.K., Larni, H.M., 1980. Drugs 20, 353–374.
Meanwell, N.A., Walker, M.A., 2008. 1,4-Diazepines. In: Katrizky, Alan, A., Ramsden, Christopher, A., Scriven, Eric, F.V., Taylor, Richard, J.K. (Eds.), Comprehensive Heterocyclic Chemistry III. Elsevier, pp. 183–235.
Pihlaja, K., Simeonov, M.F., Fülöp, F., 1997. J. Org. Chem. 62, 5080–5088.
Pulay, P., 1980. Chem. Phys. Lett. 73, 393.
Pulay, P., 1982. J. Comput. Chem. 3, 556.
Rall, T.W., 1990. In: Gilman, A.G., Rall, T.W., Nies, A.S., Taylor, P. (Eds.), Goodman and Gilman's: The Pharmaceutical Basis of Therapeutics, eighth ed. Pergamon Press, New York, p. 345.
Rudzik, A.D., Hester, J.B., Tang, A.H., Straw, R.N., Friis, W., 1973. In: Garattine, S., Mussini, E., Randall, L.O. (Eds.), The Benzodiazepines. Raven Press, New York, p. 285.
Salman, S.R., Hamdi, S.T., Ahmed, K.Y., 1986. Canadian J. Spectrosc. 31, 127–129.
Scahill, T.A., Smith, S.L., 1983. Org. Magn. Reson. 21, 621–662.
Simeonov, M.F., Fülöp, F., Sillanpää, R., Pihlaja, K., 1997. J. Org. Chem. 62, 5089–5095.
St-Amant, A., Cornell, W.D., Halgren, T.A., Kollman, P.A., 1995. J. Comput. Chem. 16, 1483.
Sternbach, L.H., Fryer, R.I., Keller, O., Metlesics, W., Sach, G., Steiger, N., 1963. J. Med. Chem. 6, 261–265.
Sternbach, L.H., Randall, L.O., Gustafson, S.A., 1964. In: Gordon, M. (Ed.), Psychopharmacological Agent, vol 1. Academic Press, New York, p. 137.
Stewart, J.J.P., 1989. J. Comput. Chem. 10, 209.
Stewart, E.L., Charles, K., Foley, C.K., Norman, L., Allinger, N.L., Bowen, J.P., 1994. J. Am. Chem. Soc. 116, 7282–7286.
Tallman, J.F., Paul, S.M., Skolnick, P., Gallager, D.W., 1980. Science 207, 274–281.
Thakur, M., Ojha, L., Thakur, A., Solanki, B.K., 2010. J. Comput Biol. Bioinformatics Res. 2, 10–19.
Venkatraj, V., Jeyaraman, R., 2006. Indian J Chem. 45B, 1531–1540.
Zahra, J.A., El-Abadelah, M.M., Nazer, M.Z., Ebraheem, K.A.K., Boese, R., 2003. Org. Biomol. Chem. 1, 1798–1801.
Zycov, B.G., Khvostenko, O.G., Khvostenko, V.I., Prokopenko, I.A., Yavorskii, A.S., Andronati, S.A., 1993. Russ. Chem. Bull. 42, 1517–1521.